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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 : A61K 31/55, 31/50, 31/495 A61K 31/505, 31/535 — A1

(11) International Publication Number: WO 90/06118

(43) International Publication Date: 14 June 1990 (14.06.90)

(21) International Application Number: PCT/US89/05505

(22) International Filing Date: 5 December 1989 (05.12.89)

(30) Priority data:
279,537 5 December 1988 (05.12.88) US

(60) Parent Application or Grant
(63) Related by Continuation
US 279,537 (CIP)
Filed on 5 December 1988 (05.12.88)

(71) Applicants *(for all designated States except US)*: HOUSTON BIOTECHNOLOGY INCORPORATED [US/US]; 3608 Research Forest Drive, The Woodlands, TX 77381 (US). E.R. SQUIBB & SONS, INC. [US/US]; P.O. Box 4000, Princeton, NJ 08543-4000 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)* : CROSSON, Craig, E. [US/US]; 25 Dovewood Place, The Woodlands, TX 77380 (US). POTTER, David, E. [US/US]; 15 West Shaker Court, The Woodlands, TX 77380 (US). ONDETTI, Miguel, A. [US/US]; 79 Hemlock Circle, Princeton, NJ 08540 (US). FLOYD, David [US/US]; Route 1, Box 404M, Lawrencevill, NJ 08648 (US). ABERG, Gunner [US/US]; 519 Bergen Street, Lawrencevill, NJ 08648 (US).

(74) Agents: DELFLACHE, Marc, L. et al.; Pravel, Gambrell, Hewitt, Kimball & Krieger, Tenth Floor, 1177 West Loop South, Houston, TX 77027 (US).

(81) Designated States: AT (European patent), AU, BB, BE (European patent), BF (OAPI patent), BG, BJ (OAPI patent), BR, CF (OAPI patent), CG (OAPI patent), CH (European patent), CM (OAPI patent), DE (European patent), DK, ES (European patent), FI, FR (European patent), GA (OAPI patent), GB (European patent), HU, IT (European patent), JP, KP, KR, LK, LU (European patent), MC, MG, ML (OAPI patent), MR (OAPI patent), MW, NL (European patent), NO, RO, SD, SE (European patent), SN (OAPI patent), SU, TD (OAPI patent), TG (OAPI patent), US.

Published
With international search report.

(54) Title: THERAPEUTIC USE OF DIHYDROPYRIMIDONES AND BENZAZEPINE AND BENZOTHIAZEPINE DERIVATIVES IN RETINAL OR OPTIC NERVE DYSFUNCTION

(57) Abstract

Ischemia or edema of the retina or optic nerve results in retinal dysfunction. This retinal dysfunction can be associated with the activation of calcium channels. The prophylactic or therapeutic administration of compounds to block these processes can ameliorate or prevent retinal dysfunction. These compounds include the dihydropyrimidones, benzazepine and benzothiazepine derivative classes selected of calcium channel antagonists. Therapeutic treatment with compounds include dihydropyrimidones and benzazepines and benzothiazepine derivatives as calcium channel antagonists. Such compounds exhibit a prophylactic effect to ischemia and edema of the retina or optic nerve.

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THERAPEUTIC USE OF DIHYDROPYRIMIDONES AND BENZAZEPINE AND BENZOTHIAZEPINE DERIVATIVES IN RETINAL OR OPTIC NERVE DYSFUNCTION

Technical Field

The subject invention is drawn to the use of dihydropyrimidones and benzazepine and benzothiazepine derivatives as calcium channel antagonists in the treatment of retinal and optic nerve dysfunction.

Background of the Invention

Retinal vascular disease and ischemia are associated with malfunction of neuroendocrine regulation and autoregulation of the choroidal and retinal circulations, respectively. It has been postulated that excessive elevation of intracellular calcium (calcium overload) in retinal blood vessels and neurons may be involved in the pathogenesis of retinal vasculopathy, ischemia and ultimately, retinal damage. Some specific pathologic events triggered by excess intracellular calcium ions include: generation of free radicals, activation of proteases, endonucleases and lipases, and interference with energy production in mitochondria.

Blood flow to the retina is supplied by two separate vascular systems: the retinal vessels supplying the inner retinal layers and choroidal vessels supplying the outer retinal layers. In primates, approximately 35% of the total retinal blood flow is derived from the retinal vessels, while 65% is from the choroidal vessels.

Although the choroidal blood flow is of greater magnitude, retinal ischemia is usually associated with a reduction of flow in the inner retinal vessels. This greater propensity for ischemia in the inner retina may result from several factors: (1) the high rate of choroidal blood flow over that required to meet the metabolic needs of the outer retina; (2) the large diameter capillaries in the choroid are less likely to be occluded by emboli; (3) the lack of anastomoses in the retinal vessels; and (4) the larger percentage of oxygen extracted from the retinal arterioles/capillaries (35%) as compared to the choroidal circulation (3-4%). To maintain an adequate supply of nutrients to the inner retina under various systemic and ocular conditions, blood flow through normal retinal vessels is highly autoregulated by metabolic (oxygen and carbon dioxide), myogenic and possibly local hormonal (paracrine and autocrine) factors.

A number of systemic and ocular disorders have been associated with ischemic conditions of the retina or optic nerve. Ocular manifestations of systemic disorders include: diabetes, atherosclerosis, hyperlipidemia, and hypertension. Specific ocular disorders include: retinitis of AIDs, macular degeneration, anterior ischemic optic neuropathy, ocular hypertension, glaucoma, retinopathy of prematurity, retinal vessel occlusion, diabetic retinopathy and hypertensive retinopathy. In addition, edemic conditions of the retina or optic nerve are evidenced in diabetes, hypertension and cystoid macular edema. Newer evidence also suggests that excessive influx of calcium ions into vascular and neuronal tissue is a primary contributor to the pathogenesis of ischemic injury and the development of vasculopathy and neuropathy.

It is therefore of substantial interest to identify compounds which may be used in the therapeutic treatment of or prophylactic treatment against vasculopathies and neuropathies associated with the eye.

Further, it is of great interest to develop a reproducible and sensitive bioassay which is a good predictor of the utility of a compound as a therapeutic for various ischemic retinopathies. Desirable characteristics of such a bioassay are the use of relatively small animals with ocular vasculature and neural retina similar to that of humans, particularly rodentiae, which provides for constitutive retinal dysfunction or the ability to reproducibly induce such dysfunction, ease of access to the major arteries supplying the retina, ease of identifying the existence of the dysfunction and the effect of addition of a candidate compound on occurrence of such dysfunction or the effect on progression of such dysfunction.

Relevant Literature

The publications cited herein are incorporated by reference as if each publication were specifically and individually indicated to be incorporated by reference.

Choi (1985) Neuroscience Letters 58:293-297, described the calcium dependence of glutamate neurotoxicity in cortical cell culture. Meldrum (1985) Clinical Science 68:113-122, describes potential therapeutic applications of antagonists of excitatory amino acid neurotransmitters. Sinclair et al., (1982) J. American Academy of Ophthalmology 89:748-750, describe retinal vascular autoregulation in diabetes mellitus. Rhie et al., (1982) Diabetes 31:1056-1060, describe retinal vascular reactivity to norepinephrine and angiotensin II in normals and diabetics. Fleckenstein et al., (1985) Am. J. Cardiol. 56:3H-14H, describe the experimental basis of long-term therapy of arterial hypertension with calcium antagonists. Fleckenstein et al., (1987) Ibid. 59:177B-187B, describe future directions in the use of calcium antagonists in the treatment of cardiovascular disease. Godfraind (1987) Ibid. 59:11B-23B, provides a classification of calcium antagonists. Fleckenstein et al., (1987) TIPS 8:496-501,

describe investigation of the role of calcium in the pathogenesis of experimental arteriosclerosis. Katz and Leach (1987) J. Clin. Pharmacol. 27:825-834, describe a therapeutic application of 1,4-dihydropyridine calcium channel blockers. Gelmers et al., (1988) N. Engl. J. Med. 318:203-207, describe an investigation of nimodipine in acute ischemic stroke. Cook and Hof (1988) Br. J. Pharmacol. 93:121-131, describe the cardiovascular effects of apamin and BRL 34915 in rats and rabbits. Nihard (1982) Angiology 33:37-45, describes the effect of calcium-entry-blockers on arterioles, capillaries and venules of the retina. Corbiere, French Patent No. 2,585,574 describes the use of ocular pharmaceuticals containing (nitrophenyl)dihydropyridinedicarboxylates. Triggle and Janis (1987) Ann. Rev. Pharmacol. Toxicol. 27:347-369, describe structure-function relationships for calcium channel ligands, particularly 1,4-dihydropyridines.

Articles concerned with rat models for chronic or acute retinal dysfunction include von Sallmann and Grimes (1974) Investigative Ophthalmology 13:1010-1015; Frank et al., (1986) Science 231:376-378 and Stefansson et al., (1988) Invest. Ophthalmol. Vis. Sci. 29:1050-1055.

SUMMARY OF THE INVENTION

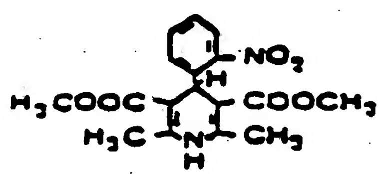
Azaheterocycle calcium entry blockers are useful in the treatment of subjects, such as mammals, including man, suffering from ischemia or edema of the retina or optic nerve. Such calcium entry blockers may be grouped as calcium channel antagonists and excitatory amino acid receptor antagonists. Associated with retinal dysfunction are techniques for assessing neural retinal function. In addition, such compounds exhibit prophylactic effects in preventing such conditions. Methods are further provided for screening compounds associated with regulation of calcium channels by employing in vivo bioassays using rats with inducible retinal dysfunction.

DESCRIPTION OF THE SPECIFIC EMBODIMENTS

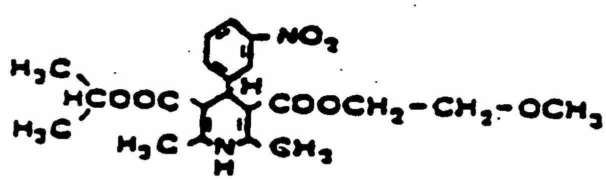
Compounds associated, either directly or indirectly, with the modulation of calcium entry exhibit a therapeutic or prophylactic effect to subjects suffering from ischemia or edema of the retina or optic nerve. Such conditions are evidenced in the systemic and ocular ischemic and edemic disorders cited above.

These compounds may be divided into two categories. The first are the calcium channel antagonists, which may be further divided into dihydropyridines, dihydropyrimidones, diphenylpiperazines, benzazepines and benzothiazepines derivatives. The second category are excitatory amino acid antagonists, which include NMDA, quisqualate and kainate receptor antagonists.

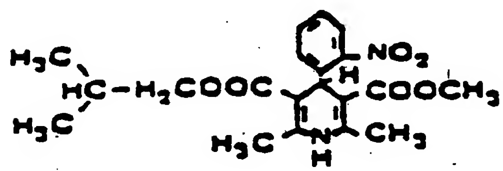
Among dihydropyridines of interest are nifedipine, having the structural formula:



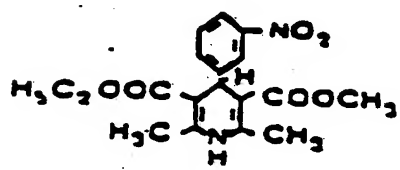
nimodipine, having the structural formula:



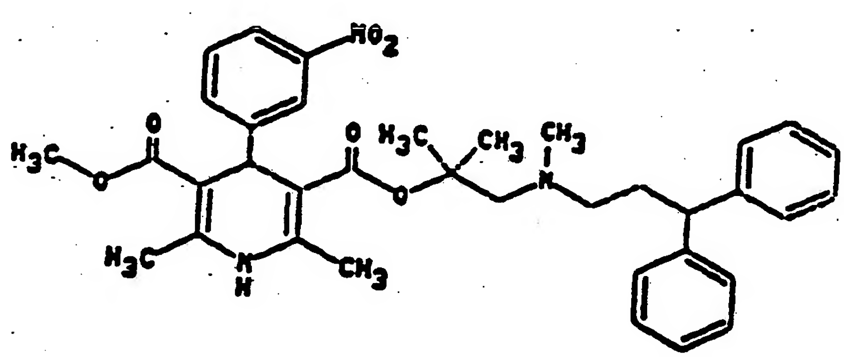
nisoldipine, having structural formula:



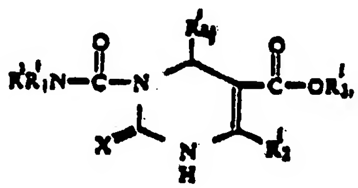
nitrendipine, having structural formula:

 ; and

1,1-Dimethyl-2-[N-(3,3-diphenylpropyl)-N-methyl-amino]ethyl methyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridinedicarboxylate hydrochloride, having the structural formula:

 .HCl

Among dihydropyrimidones are those of the formula:



and pharmaceutically acceptable salts thereof wherein X is oxygen or sulfur; R' is hydrogen, alkyl, cycloalkyl, aryl, or arylalkyl and R'_1 is hydrogen, alkyl, cycloalkyl, aryl, heterocyclo,

$$-\underset{R'_6}{\overset{R'_5}{\underset{|}{\overset{|}{C}}}}-(CH_2)_n-Y_2-\underset{R'_6}{\overset{R'_5}{\underset{|}{\overset{|}{C}}}}-(CH_2)_p-Y_3$$

or halo substituted alkyl, or R' and R'_1 taken together with the nitrogen atom to which they are attached are 1-pyrrolidinyl, 1-piperidinyl, 1-azepinyl, 4-morpholinyl, 4-thiamorpholinyl, 1-piperazinyl, 4-alkyl-1-piperazinyl, 4-arylalkyl-1-piperazinyl, 4-diarylalkyl-1-piperazinyl or 1-pyrrolidinyl, 1-piperidinyl, or 1-azeipinyl substituted with alkyl, alkoxy, alkylthio, halo, trifluoromethyl or hydroxy;

R'_2 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl,

$$-\underset{R'_6}{\overset{R'_5}{\underset{|}{\overset{|}{C}}}}-(CH_2)_n-Y_1,$$

or halo substituted alkyl;

R'_3 is hydrogen, alkyl, cycloalkyl, aryl, heterocyclo,

$$-\underset{R'_6}{\overset{R'_5}{\underset{|}{\overset{|}{C}}}}-(CH_2)_n-Y_2, -\underset{R'_6}{\overset{R'_5}{\underset{|}{\overset{|}{C}}}}-(CH_2)_p-Y_3,$$

or halo substituted alkyl;

R'_4 is aryl or heterocyclo;

R'_5 and R'_6 are each independently hydrogen, alkyl, $-(CH_2)_q-$aryl or $-(CH_2)_q-$cycloalkyl;

Y_1 is cycloalkyl, aryl, heterocyclo, hydroxyl, alkoxy, aryl $-(CH_2)_m-O-$, mercapto, alkylthio, aryl$-(CH_2)_m-S-$, amino, substituted amino, carbamoyl,

(Substituted amino)$-\overset{O}{\overset{\|}{C}}-$, heterocyclo$-(CH_2)_m-\overset{O}{\overset{\|}{C}}-$

carboxyl, alkoxycarbonyl, alkyl$-\overset{O}{\overset{\|}{C}}-$, aryl$-(CH_2)_m)-\overset{O}{\overset{\|}{C}}-$

alkyl$-\overset{O}{\overset{\|}{C}}-O-$ or aryl$-(CH_2)_m-\overset{O}{\overset{\|}{C}}-O-$

Y_2 is cycloalkyl, aryl, heterocyclo, carbamoyl,

(substituted amino)$-\overset{O}{\overset{\|}{C}}-$, carboxyl, alkoxycarbonyl,

alkyl$-\overset{O}{\overset{\|}{C}}-$, aryl$-(CH_2)_m-\overset{O}{\overset{\|}{C}}-$ or heterocyclo$-(CH_2)_m-\overset{O}{\overset{\|}{C}}-$;

Y_3 is hydroxyl, alkoxy, aryl$-(CH_2)_m-O-$, mercapto, alkylthio, aryl$-(CH_2)_m-S-$,

alkyl$-\overset{O}{\overset{\|}{C}}-O-$, aryl$-(CH_2)_m-\overset{O}{\overset{\|}{C}}-O-$,

amino or substituted amino;

q is 0, 1, 2 or 3;

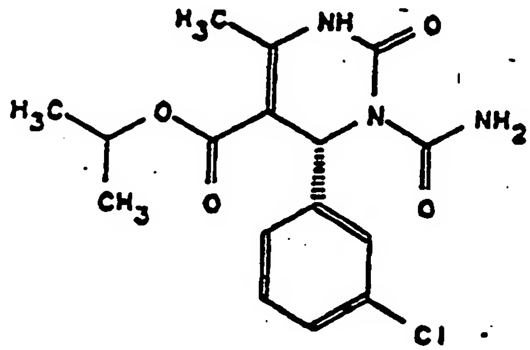
m is 0 or an integer of 1 to 6;

n is O or an integer of 1 to 5; and

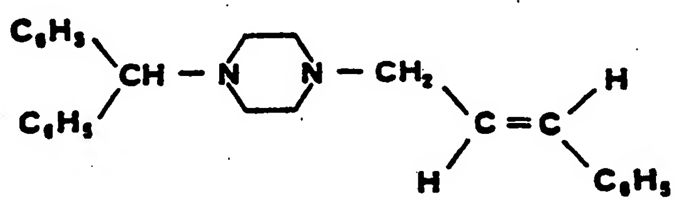
p is an integer of 1 to 5.

Especially preferred is (R)-1-(Aminocarbonyl)-6-(3-chlorophenyl)-1,2,3,6-tetrahydro-4-methyl-2-oxo-

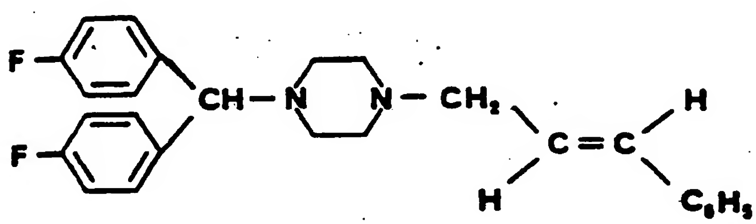
5-pyrimidine-carboxylic acid, 1-methylethyl ester, having the structural formula:



Among diphenylpiperazines of interest are cinnarizine and flunarizine, having structural formula:



and

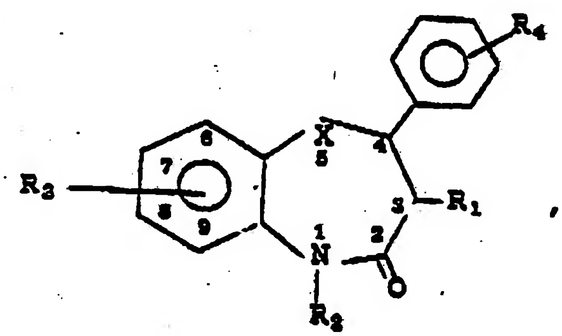


In addition, the calcium entry blockers of this invention may include such calcium channel antagonists as

phenylalkylamines, such as verapamil and adipamil, benzothiazepines, such as diltiazem, clentiazem and naltiazem and benzazepines.

Benzazepine and benzothiazepine derivatives of interest include those of the formula:

I.



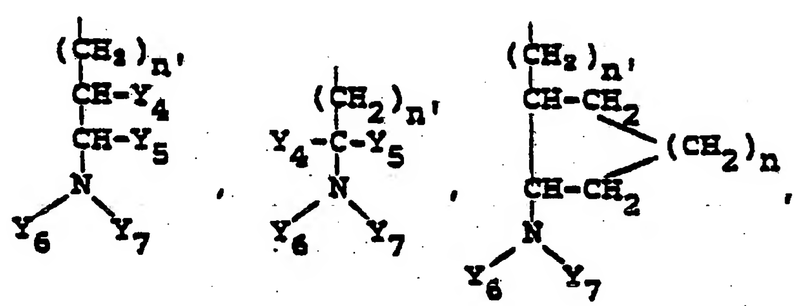
I

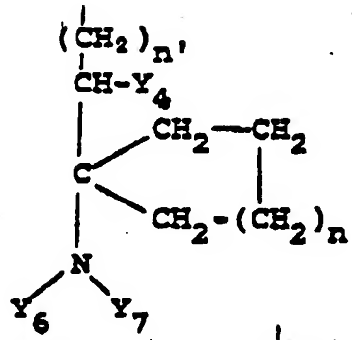
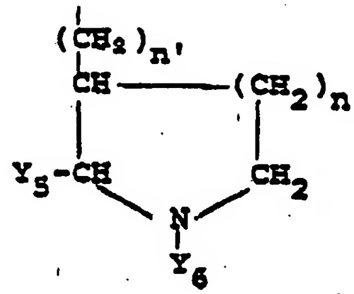
and the pharmaceutically acceptable salts thereof, wherein:

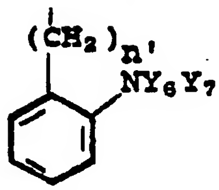
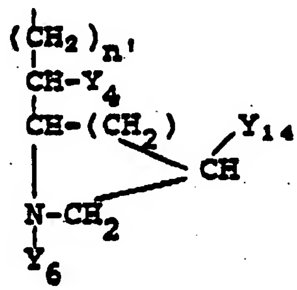
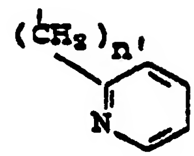
X is $-CH_2-$ or $-S-$;

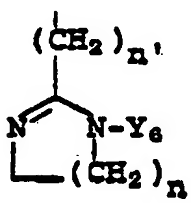
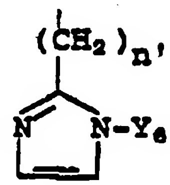
R_1 is $-\underset{Y_2}{\overset{Y_1}{CH}}$ or $-O-Y_3$;

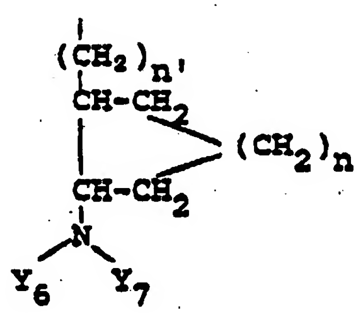
when X is $-CH_2-$, R_2 is

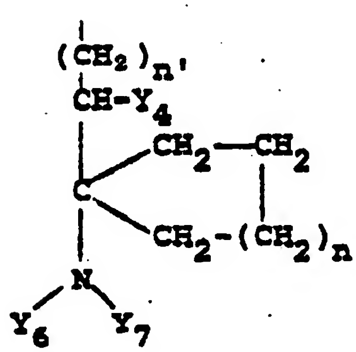
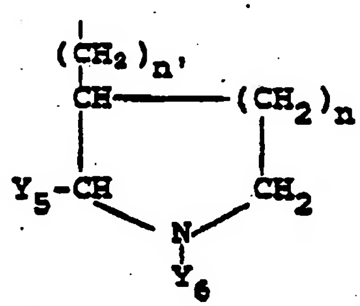


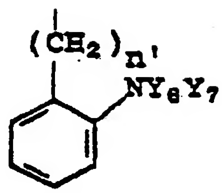
 ,  ,

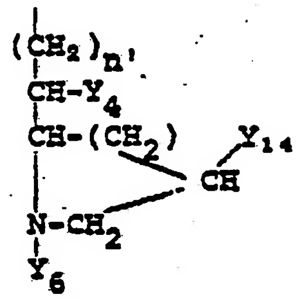
 ,  , 

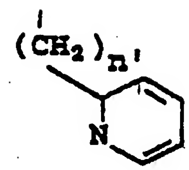
 , or  ;

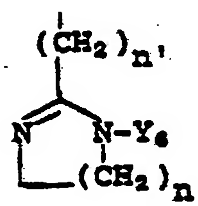
when X is -S-, R_2 is  ,

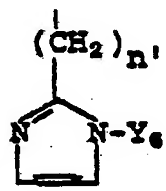
 , 

 ,

 ,



 , or

 ;

R_3 and R_4 are each independently hydrogen, halogen, alkyl, alkoxy, aryloxy, arylalkoxy, arylalkyl, cyano, hydroxy, alkanoyloxy,

$-O-\overset{O}{\overset{\|}{C}}-NY_8Y_9$, fluoro substituted alkoxy, fluoro substituted alkyl, (cycloalkyl)alkoxy, $-NO_2$,

$-NY_{10}Y_{11}$, $-S(O)_m$alkyl, $-S(O)_m$aryl, $-\overset{O}{\overset{\|}{C}}-Y_{12}$ or

$-O-\overset{O}{\overset{\|}{C}}-Y_{13}$;

n or n' are independently 0, 1, 2, or 3;

m is 0, 1 or 2;

Y_1 and Y_2 are independently hydrogen or alkyl, Y_1 is hydrogen and Y_2 is alkenyl, alkynyl, aryl, heteroaryl, or cycloalkyl, or Y_1 and Y_2 together with the carbon atom to which they are attached are cycloalkyl;

Y_3 is hydrogen, alkyl, alkanoyl, alkenyl, arylcarbonyl, heteroarylcarbonyl, or $-\overset{O}{\overset{\|}{C}}-NY_8Y_9$;

Y_4 and Y_5 are each independently hydrogen, alkyl, aryl or arylalkyl, provided that when both are present they are not both hydrogen, and provided further that when both are attached to the same carbon atom neither of them is hydrogen;

Y_6 and Y_7 are each independently hydrogen, alkyl, cycloalkyl or arylalkyl or Y_6 and Y_7 together with the nitrogen atom to which they are attached are azetidinyl, pyrrolidinyl, piperidinyl, or morpholinyl;

Y_8 and Y_9 are each independently hydrogen, alkyl, aryl or heteroaryl, or Y_8 and Y_9 together with the nitrogen atom to which they are attached are pyrrolidinyl, piperidinyl or morpholinyl;

Y_{10} and Y_{11} are each independently hydrogen, alkyl, alkanoyl, arylcarbonyl, heteroarylcarbonyl,

or $-\overset{\overset{\large O}{\|}}{C}-NY_8Y_9$;

Y_{12} is hydroxy, alkoxy, aryloxy, amino, alkylamino or dialkylamino;

Y_{13} is alkyl, alkoxy, or aryloxy; and

Y_{14} is hydrogen, hydroxy, alkoxy, aryloxy or arylalkoxy.

Listed below are definitions of various terms used to describe the compounds of this invention. These definitions apply to the terms as they are used throughout the specification (unless they are otherwise limited in specific instances either individually or as a part of a larger group.)

The terms "alkyl" and "alkoxy" refer to both straight and branched chain groups. Those groups having 1 to 10 carbon atoms are preferred.

The term "alkenyl" refers to both straight and branched chain groups. Those groups having 2 to 10 carbon atoms are preferred.

The term "aryl" refers to phenyl and substituted phenyl. Exemplary substituted phenyl groups are phenyl groups substituted with 1, 2 or 3 amino ($-NH_2$), alkylamino, dialkylamino, nitro, halogen, hydroxyl, trifluoromethyl, alkyl (of 1 to 4 carbon atoms), alkoxy (of 1 to 4 carbon atoms), alkylthio, (of 1 to 4 carbon atoms), alkanoyloxy, carbonyl, or carboxyl groups.

The term "alkanoyl" refers to groups having the formula $\text{alkyl}-\overset{\displaystyle O}{\overset{\|}{C}}-$. Those alkanoyl groups having 2 to 11 carbon atoms are preferred.

The term "heteroaryl" refers to an aromatic heterocyclic group having at least one heteroatom in the ring. Preferred groups are pyridinyl, pyrrolyl, imidazolyl, furyl, thienyl, oxazolyl or thiazolyl.

The term "cycloalkyl" refers to groups having 3, 4, 5, 6 or 7 carbon atoms.

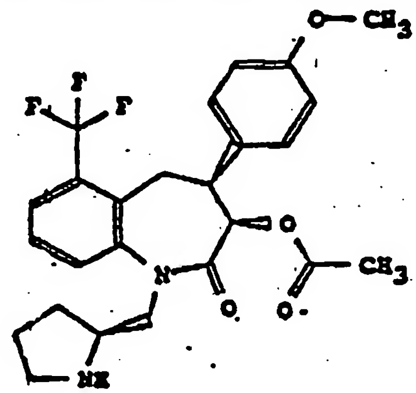
The term "halogen" refers to fluorine, chlorine, bromine and iodine.

The terms "fluoro substituted alkyl" and "fluoro substituted alkoxy" refer to alkyl and alkoxy groups (as described above) in which one or more hydrogens have been replaced by fluorine atoms. Exemplary groups are trifluoromethyl, 2,2,2-trifluoroethyl, pentafluoroethyl, fluoromethoxy, difluoromethoxy, etc.

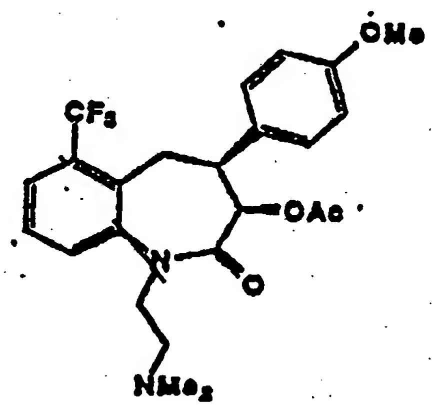
The compounds of formula I form acid-addition salts with inorganic and organic acids. These acid-addition salts frequently provide useful means for isolating the products from reaction mixtures by forming the salt in a medium in which it is insoluble. The free base may then be obtained by neutralization, e.g., with a base such as sodium hydroxide. Any other salt may then be formed from the free base and the appropriate inorganic or organic acid. Illustrative are the hydrohalides, especially the hydrochloride and hydrobromide, sulfate, nitrate, phosphate, borate, acetate, tartrate, maleate, citrate, succinate, benzoate, ascorbate, salicylate, methanesulfonate, benzenesulfonate, toluenesulfonate and the like.

The carbon atoms in the 3 and 4-positions of the benzazepine nucleus and, carbon atoms in the 2 and 3-positions of the benzothiazepine nucleus, of the compounds of the formula I are asymmetric carbons. The compounds of formula I, therefore, exist in enantiomeric and diastereomeric forms and as racemic mixtures thereof. All are within the scope of this invention. It is believed that those compounds of formula I which have the cis configuration are the most potent and are therefore preferred.

Particularly preferred as a suitable benzazepines within this invention is the compound [3R-[1(S*),3<a,4<a]]-3-(Acetyloxy)-1,3,4,5-tetrahydro-4-(4-methoxyphenyl)-1-(2-pyrrolidinyl-methyl)-6-(trifluoromethyl)-2H-1-benzazepin-2-one, monohydrochloride having the structural formula:

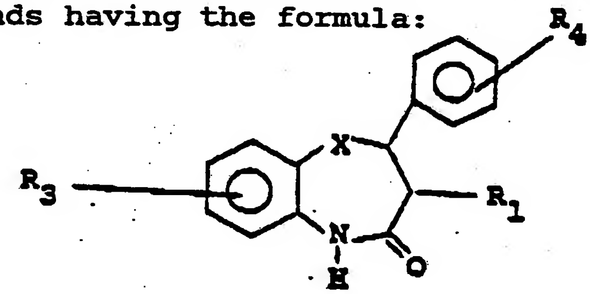


Additionally, compounds disclosed in U.S. Patent No. 4,748,239 including (3R-<u>cis</u>)-3-(Acetyloxy)-1-[2-(dimethylamino)ethyl]-1,3,4,5-tetrahydro-4-(4-methoxyphenyl)-6-(trifluoromethyl)-2H-1-benzazepin-2-one, monohydrochloride the structure:



are useful herein.

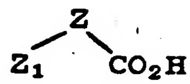
Calcium channel antagonists which may be employed in this invention are produced by conventional methods well known in the art. In particular the benzothiazepine and benzazepine derivatives can be prepared from the corresponding compounds having the formula:

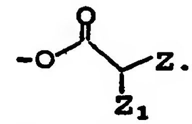


The preparation of the racemic and nonracemic forms of the compounds of formula II when X is CH_2 is described in United States Patent 4,752,645 issued June 21, 1988 for those compounds wherein R_1 is $-\underset{\underset{Y_2}{|}}{\overset{\overset{Y_1}{|}}{C}}H$, and in United States Patent 4,748,239, issued May 31, 1988 for those compounds whrein R_1 is $-OY_3$ and Y_3 is hydrogen. Compounds of formula II where X is S and R_1 is OY_3 are prepared as described in U.S. Patent 3,562,257 issued February 9, 1971.

Compounds of formula II where X is S and R_1 is $-\underset{\underset{Y_2}{|}}{\overset{\overset{Y_1}{|}}{C}}H$ are prepared as described in U.S. Patent 4,694,002, issued September 15, 1987. Compounds of formula II wherein R_1 is $-O-Y_3$ and Y_3 is other than hydrogen can be obtained by alkylation or acylation (using conventional techniques) of the corresponding compound of the formula II wherein R_1 is $-OH$.

The compounds of formula II where R_1 is OH can be prepared in nonracemic form by reacting the racemic compound of formula II where R_1 is OH with a nonracemic

acid or amino acid  where Z and Z_1 are different, using conventional acylation techniques such as carbodiimide with a catalyst such as dimethylaminopyridine, to give a mixture of

diastereomeric compounds II whrein R_1 is 

This mixture of diastereomeric compounds can be separated by those skilled in the art, using chromatographic techniques or crystallization. The nonracemic compounds of formula II where R_1 is OH are obtained from the purified diastereomers by hydrolysis with a base such as sodium hydroxide or sodium methoxide.

Treatment of a compound of formula II with a base (e.g., sodium hydride or cesium carbonate) in an inert solvent (e.g., dimethylformamide or dimethylsulfoxide) followed by reaction with a compound of the formula:

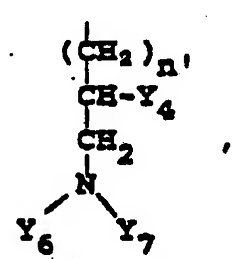
III R_2-L

(where L is a leaving group such as halo or tosyloxy) yields the corresponding product of formula I.

Alternatively, a compound of formula I can be prepared by reacting a compound of formula II with one of formula III under phase transfer conditions in a mixture of water and dichloromethane or toluene in the presence of an appropriate base (e.g., barium hydroxide or sodium hydroxide) and catalyst (e.g., benzyl trimethylammonium chloride or tetra-n-butylammonium hydrogen sulfate).

Alternatively, the products of formula I wherein R_1 is -OH can be alkylated or acylated (using conventional techniques) to obtain those products of formula I wherein R_1 is $-O-Y_3$ and Y_3 is other than hydrogen.

An additional procedure for preparing the compounds of formula I wherein R_2 is:

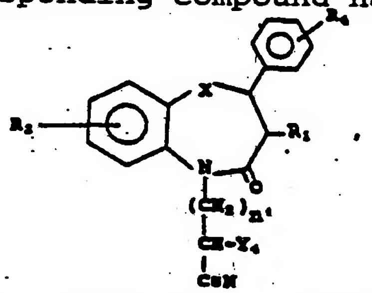


comprises treating a compound of formula Ii with an alkali metal hydride (e.g., sodium hydride) in an inert solvent (e.g., dimethylformamide or dimethylsulfoxide) followed by reaction with a compound of the formula:

IV. $L-(CH_2)_{n'}-\overset{\overset{\Large Y_4}{|}}{C}H-C=N$

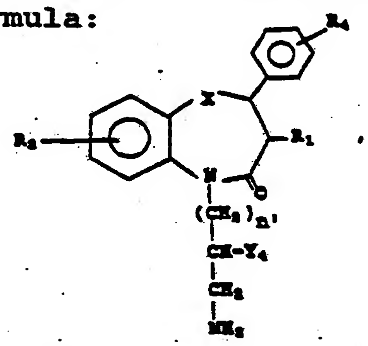
to obtain the corresponding compound having the formula:

V.



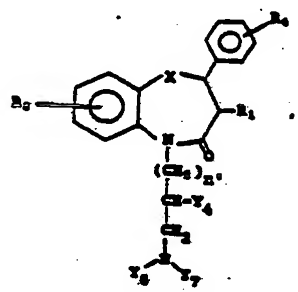
Reduction of a compound of formula V using, for example, catalytic hydrogenation (e.g., rhodium on alumina) yields the corresponding product of formula I having the formula:

VI.



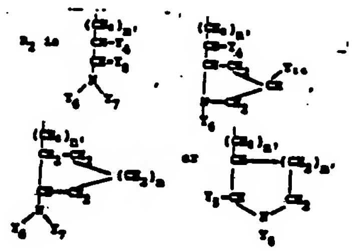
Reductive amination of a compound of formula VI with the appropriate aldehyde or ketone using a chemical reducing agent (e.g., sodium cyanoborohydride) yields the corresponding product of formula I having the formula:

VII.



wherein at least one of Y_6 and Y_7 is other than hydrogen.

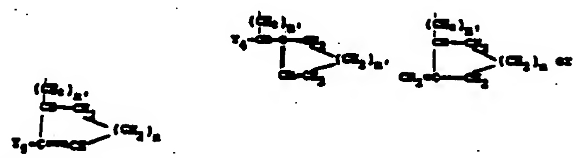
Alternatively, compounds of formula I whrein



can be prepared by first treating a compound of formula II with an alkali metal hydride (e.g., sodium hydride) in an inert organic solvent (e.g., dimethylformamide or dimethylsulfoxide) followed by reaction with the appropriate compound having the formula:

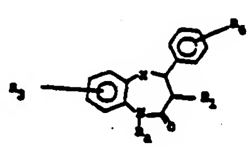
VIII R_a-L

wherein R_a is $Y_4-\overset{|}{\underset{|}{\overset{(CH_2)_{n'}}{}}}CH-\underset{\underset{CH_2}{\|}}{C}-Y_5$,



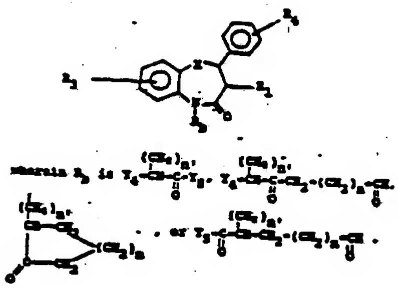
The resultant compound has the formula:

IX.



and can be reacted with ozone in an inert solvent (e.g., a halogenated hydrocarbon) followed by reduction (e.g., using a chemical reducing agent such as dimethylsulfide) to yield the corresponding compound having the formula:

X.

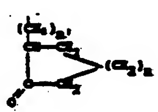


A compound of formula X can be treated with the appropriate amine having the formula:

XI. HNY_6Y_7

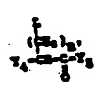
in the presence of a reducing agent (e.g., hydrogen using a catalyst such as palladium on carbon, or a chemical reducing agent such as sodium cyanoborohydride) to obtain the corresponding product of formula I.

It is also possible to obtain an intermediate of formula X wherein R_b is $Y_4-\underset{\displaystyle |}{\overset{(CH_2)_{n'}}{CH}}-\underset{\displaystyle \overset{\|}{O}}{C}-Y_5$ or

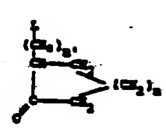


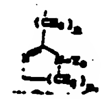
by reacting a compound of formula II with a compound of the formula:

XIIa.



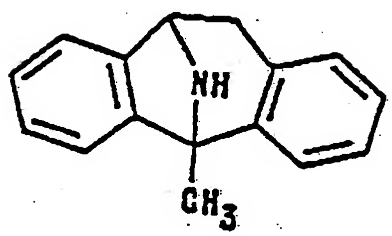
XIIb.

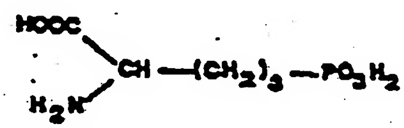


Compounds of formula I wherein R_2 is  can be synthesized by reaction of a compound of formula II with an alkylating agent, such as chloroacetonitrile to to give a compound of formula I wherein R_2 is $-CH_2CN$. The resultant compound of formula I wherein R_2 is $-CH_2CN$ can be reacted with an alcohol, such as ethanol in the presence of a catalyst, such as hydrochloric acid or sodium ethoxide to give a compound of formula I wherein R_2 is $-CH_2\underset{\mid}{C}=NH$ with OEt on the carbon, i.e. $-CH_2C(OEt)=NH$. Treatment of this compound with a diamine of the formula $H_2N-CH_2(CH_2)_nNHY_6$ gives compounds of formula I wherein R_2 is .

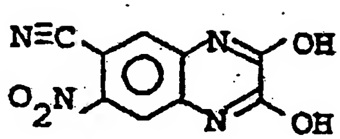
Illustrative compounds within this invention are those wherein R_3 is located in the 6- or 7- position of the benzazepine nucleus or the 8- or 9- position of the benzothiazepine nucleus and is halogen, trifluoromethyl or methoxy; and R_4 is located in the 4-position of the phenyl ring to which it is attached and is alkoxy. Included herein are compounds wherein R_3 is 6-trifluoromethyl or 7-methoxy on the benzazepine nucleus, or 8-methoxy on the benzothiazepine nucleus, and R_4 is methoxy.

Excitatory amino acid receptor antagonists include MK-801, 2-APV and CNQX, having the structural formula:





and



respectively.

Further, the pharmaceutically acceptable salts of any of the above-designated compounds may be employed as the calcium entry blocker in accordance with the invention. Combinations of the aforementioned compounds may likewise be used.

Calcium entry blockers of this invention may be administered orally, parenterally or topically. In acute situations, parenteral and/or topical administration is preferred in order to more rapidly introduce the calcium

entry blocker to the target site. For chronic therapy, oral administration is normally preferred since it is more easily administered.

The compounds for use in this invention are administered in their pure form or in admixture with a pharmaceutically acceptable carrier such as an organic or inorganic solid or liquid excipient (depending on the desired administration). The pharmaceutical preparations may thus be administered as a solid, semi-solid, lyophilized powder, liquid dosage form, tablets, pills, capsules, powders, solutions, suspensions, emulsions, creams, lotions, ointments, or granules, as well as injectable solutions. The nature of the composition in the pharmaceutical carrier or diluent will, of course, depend upon the intended route of administration.

When the pharmaceutical composition is in the form of a solution or suspension, examples of appropriate pharmaceutical carriers or diluents (depending on the intended route of administration) include for aqueous systems, water; for non-aqueous systems, ethanol, glycerin, propylene glycol, corn oil, olive oil, syrup, cottonseed oil, peanut oil, sesame oil, parafins and mixtures thereof with water; and for solid systems, lactose, kaolin, mannitol, sucrose, gelatin and agar.

In addition to conventional pharmaceutical carriers or excipients, the pharmaceutical compositions may include other medicinal agents, pharmaceutical agents, adjuvants, stabilizers, anti-oxidents, preservatives, lubricants, suspending agents, and viscosity modifiers, etc.

The dosage level of the calcium entry blocker within this invention is dependent upon the conditions of the disease to be treated, the administration route employed, the subject and the pharmacokinetic and pharmacodynamic characteristics of the active ingredient. The dosage of the active ingredient is generally within the range from about 0.1 to about 100 mg/kg administered orally, parenterally or topically.

When administered either parenterally or topically, the physiological pH is generally in the range of about pH 6.5 to 8.

Methods are further described for screening compounds capable of reversing retinal malfunction the effect of retinal dysfunction, where an *in vivo* bioassay is employed involving rats with inducible retinal dysfunction. Specific compounds for treating retinal dysfunction are provided associated with modulation of calcium channel activity and/or the activation of excitatory amino acid receptors. Particularly, calcium channel antagonists or other compounds having equivalent effect (excitatory amino acid antagonists) can be used in the treatment of retinal vasculopathy.

One methodology involves the use of Dahl salt-sensitive (SS) rats which are available from Harlan Sprague-Dawley. The rats will generally be in the age group of three to twenty weeks, usually in the age group of four to twelve weeks. When placed on a high salt diet, the animals rapidly develop (2-4 weeks) a systemic hypertension. Other rats which may be used are normal Sprague-Dawley (albino) rats, Long-Evans pigmented rats or spontaneously hypertensive (SHR) (albino) rats.

All of these rats may be employed as models by creation of acute retinal ischemia in their eyes. The ischemia may be created by reversibly occluding the short posterior ciliary arteries and the central retinal artery. Electroretinograms are recorded prior to, during and after occlusion. The occlusion is reversed after a brief period, usually one minute to three hours, preferably five minutes to two hours and reperfusion occurs. During reperfusion ERGs are taken to provide an index of retinal function, followed by a histologic examination to determine changes in normal retinal structure. Ophthalmoscopic examination of the eyes is also performed to document the absence of retinal blood flow and gross ischemic damage. Drug efficacy is related to the ability

of the candidate composition to reduce or prevent pathologic changes noted in ERG and histologic examinations.

For histological examination, the eyes may be fixed by cardiac perfusion with a fixative, such as a combination of paraformaldehyde and glutaraldehyde in an appropriate buffer. After removal of the eyes, the globe may be opened at the ora serrata and fixation continued for four to twenty-four hours. Segments of the central and peripheral retinal are then dissected free, the tissue washed and then post fixed in an appropriate fixative, e.g., osmium tetroxide. Following dehydration, the sample may be sectioned in accordance with conventional techniques for light and electron microscopy.

Changes in thickness on the retinal layer or number of cell bodies per unit area in the inner and outer nuclear layers may then be observed and reported. In addition, the retinas may be reported as "normal", if all layers are intact with no abnormalities; "mild degeneration", if thinning of the inner and outer segments or visible reduction in cell bodies of the inner and outer nuclear layers has occurred; and "severe degeneration", if extensive loss of any individual or multiple layers of the retina has occurred.

To evaluate retinal function, an electroretinogram (ERG) may be employed. Functional assessment of the inner and outer layers of the neural retina and the non-neural retina (RPE) is made by means of full field ERGs. The wave forms of the ERG result from the electrophysiological processes involved in visual transduction in the retina. Reduction in these waves provides a direct measurement of retinal function. The initial negative deflection, termed the "a-wave", originates in the photoreceptors. The subsequent b-wave is produced by the Muller and bipolar cells from the inner retina. The much slower positive c-wave arises from the RPE but is generally reduced or absent in adult albino rats. Whereas the photoreceptors

and RPE are nourished by the choroidal circulation, the Muller and bipolar cells are nourished primarily by the retinal vessels. An initial indication as to the site of retinal ischemia may be related to selective reductions in the individual wave forms.

Base-line ERGs may be obtained prior to induction of retinal ischemia. Thereafter, ERGs are determined at convenient intervals, e.g. hourly, daily or weekly. These subsequent ERGs are then normalized to preischemic values and are expressed as the percent of control (i.e. baseline) values. Prior to dark adaptation, the rat host receives an ophthalmoscopic examination to ensure the absence of cataracts or other gross abnormalities. Since rats are primarily a rod-dominated (98%) animal, ERGs are performed under dark-adapted conditions (12-14 hours). Rats are anesthetized and placed on a heating pad to maintain normal body temperature.

To record ERGs, small agar-Ag/AgCl electrodes are placed on the cornea and tongue. A reference ground electrode is placed under the scalp. ERG signals may be amplified by an appropriate differential amplifier and recorded. Light stimulation is provided by an appropriate photostimulator in conjunction with a series of neutral density filters.

Single flash (10 μsec duration) of white light is used to generate individual ERGs. The amplitude of the b-waves is measured from base line to peak in the absence of an a-wave or from the trough of the a-wave to the peak of the b-wave. a-Waves are measured form the base line to the peak of the a-wave. The time interval from the onset of the flash to the peak of the a- and b-waves is used for measurements of latency.

Group data are compared by means of a two-way analysis of variance. Comparisons involving two means employ Students t-test for non-paired data. Differences between groups (control vs. drug-treated) are regarded as significant if P-values are ≤ 0.05.

The following examples are offered by way of illustration and not by way of limitation.

EXPERIMENTAL

The methodology involves the creation of acute retinal ischemia in the eyes of normal Sprague-Dawley (albino) or Long-Evans (pigmented) rats, which are available from Harlan Sprague-Dawley. Adult rats were used, ranging in weight from 175 g to 250 g. These rats were housed under normal conditions and fed standard rat chow. Rats were anesthetized with 50 mg/kg sodium pentobarbital intraperitoneally (i.p.) and the iris of the eye dilated with one drop of 10% atropine solution. Total retinal ischemia in these animals was created by reversibly occluding the short posterior ciliary arteries and the central retinal artery. The duration of the occulsions varied from five to 120 minutes. Prior to the occlusion, baseline ERGs were recorded and used as an index of normal retinal function. Complete retinal occlusion was determined by the absence of ERG. At the end of the occlusion period, the retina was allowed to reperfuse, and changes in normal retinal structure and function determined by histological observations and ERGs. During the reperfusion period, ERGs were evaluated at one to two minute intervals for the first 30 minutes and thereafter at ten minute intervals through 120 minutes. Additional, ERG evaluations in selected animals were made at 24 hours. Drug efficacy was based on the ability of a compound to minimize or prevent the pathologic changes in retinal structure and/or function induced by acute retinal ischemia (e.g. the appearance of necrotic cells within the retina or a significant reduction or loss of normal wave forms in the ERG.)

Example 1 illustrates an in vivo bioassay which can be employed for determining the efficacy of compounds in the treatment of retinal dysfunction.

Examples 2-4, conducted in accordance with the procedure of Example 1, demonstrate that pretreatment with

Ca^{++} channel antagonists can protect retinal function (as measured by ERG recovery) from ischemic injury. Values are means ± standard errors and have been normalized (0-100%) to preocclusion control values. At each time point tested, significant improvement in b-wave recovery when compared to control-treated animals is exhibited.

Example 5 is drawn to the use of an excitatory amino acid antagonist.

Example 1

The subject invention provides for retinal degeneration models as evidenced by both structural and functional changes. Associated with the retinal dysfunction and/or degeneration is a dramatic reduction in retinal perfusion. These rats are therefore good models for screening compounds having activities as calcium channel antagonists or excitatory amino acid antagonists and their use in preventing or ameliorating retinal degeneration.

Four different periods of retinal ischemia in Long-Evans and Sprague-Dawley rats were examined. In normal Sprague-Dawley rats occlusions of five minutes resulted in the rapid return to control level of both a- and b-waves of the ERG, while occlusions of two hours result in the irreversible loss of retinal function, as measured by the ERG. Occlusion for periods between five minutes to two hours in both Long-Evans and Sprague-Dawley rats resulted in a partial but permanent loss of retinal function, that was amenable by drug therapy.

Reperfusion following 30 minutes of total retinal ischemia resulted in rapid recovery of the a-wave in one to two minutes. The recovery of the b-wave was considerably different. The b-wave was first observed between 16 and 22 minutes. From this point the b-wave slowly recovered over the next 60 to 120 minutes, but remained significantly reduced from the control levels. By 120 minutes, the b-wave has recovered to approximately 30% of control values. By 24 hours the mean b-wave was

still only 40% of control values. For shorter periods of occlusion (e.g. 15 minutes), the a-wave again rapidly recovered in one to two minutes. The initial appearance of the b-wave also occurred at 16 to 22 minutes of reperfusion, but the magnitude of the a-wave recovery at 90 minutes and 24 hours was 61% and 100% of control levels (as compared to 26% and 40%, respectively, for the 30 minute occlusion). These data indicate that total retinal ischemia for 30 minutes results in the partial loss of retinal function. This loss appears to be permanent, as the b-wave recovery was only 40% of control values after 24 hours of reperfusion. The rapid return of the a-wave and gradual return of the b-wave indicates that the primary site of acute retina ischemic injury is the inner retinal layer.

Example 2

Long-Evans rats were treated i.p. with control (10% TWEEN 80) or nifedipine 30 minutes prior to the occlusion of retinal vessels.

Table I shows the effect of nifedipine i.p. on b-wave recovery following 30 minutes of total retinal ischemia (*P<0.05).

TABLE I

TIME FROM REPERFUSION (min)	CONTROL (N=7)	1 mg/kg (n=4)	3.3 mg/kg (n=5)	10 mg/kg (n=6)	33 mg/kg (n=5)
30	5 ± 2	13 ± 3*	20 ± 6*	13 ± 2*	15 ± 5*
60	19 ± 4	47 ± 2*	60 ± 9*	39 ± 5*	41 ± 6*
90	28 ± 6	66 ± 2*	81 ± 12*	58 ± 9*	51 ± 6*
120	32 ± 6	72 ± 2*	84 ± 13*	65 ± 11*	54 ± 6*
180	34 ± 5	70 ± 5*	81 ± 9*	67 ± 9*	53 ± 6*

The ability of the 3.3 mg/kg dose to provide apparently better protection of retinal function than the 10 and 33 mg/kg dose likely reflects cardiovascular side effects of nifedipine, as significantly greater reductions in heart rate and blood pressure were observed in these animals. Hence, the resulting dose-related reduction in cardiac output and peripheral vasodilation likely reduces

retinal perfusion in the ischemic eye and reduces functional recovery (e.g. ERG's) of the retina.

Example 3

Long-Evans rats were treated intraperitoneally with either 10% TWEEN 80 as a control or 1,1-Dimethyl-2-[N-(3,3-diphenylpropyl)-N-methyl-amino]ethyl methyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridine-dicarboxylate hydrochloride 30 minutes prior to the occlusion of retinal vessels. Statistical comparisons were made and the results tabulated at each time point. (*P<0.05).

TABLE II

TIME FROM REPERFUSION (min)	CONTROL (n=7)	0.33 mg/kg (n=5)
30	7.0 ± 2	13 ± 5*
60	19 ± 3	36 ± 6*
90	31 ± 2	52 ± 5*
120	35 ± 2	60 ± 3*
180	36 ± 6	64 ± 4*

Example 4

Long-Evans rats were treated with either water (as control) or [3R-[1(S*),3<a,4<a]]-3-(Acetyloxy)-1,3,4,5-tetrahydro-4-(4-methoxyphenyl)-1-(2-pyrrolidinyl-methyl)-6-(trifluoromethyl)-2H-1-benzazepin-2-one, monohydrochloride 30 minutes prior to the occlusion of retinal vessels. Statistical comparisons were made at each time point. See Table III. (*P<0.05).

TABLE III

TIME FROM REPERFUSION (min)	CONTROL (n=6)	3.3 mg/kg (n=5)
30	4 ± 1	11 ± 1*
60	21 ± 2	36 ± 4*
90	28 ± 2	54 ± 2*
120	37 ± 2	63 ± 4*
180	42 ± 2	74 ± 4*

Example 5

Unlike Ca^{++} channels, which are located in both retinal neurons and vessels, excitatory amino acid receptor are located only in the retina. Hence, the *in vitro* chick retina assay, an assay independent of retinal blood flow, was used to evaluate these excitatory amino acid receptor antagonists. Chick retinas were isolated from a day 14 embryo. Isolated retinas were then incubated for 40 or 60 minutes in a control Ringer's solution (5 mM glucose under an atmosphere of 95% air, 5% CO_2) or in a test Ringer's solution (0 mM glucose under an atmosphere of 95% N_2, 5% CO_2). In selected experiments, the NMDA antagonist, MK 801 (10^{-6} to 10^{-4}M), was added to retinas incubated in the test Ringer's solution. At the end of the incubation period retinas were fixed in 4% paraformaldehyde, dehydrated in ethanol and embedded in paraffin. Thick (4μm) cross-section of the retina were then cut, stained with haematoxylin and eosin, and evaluated by light microscopy to determine the degree of retinal degeneration.

Control retinas (i.e. incubate in Ringer's with glucose under 95% air) showed no damage or alteration in retinal structure following incubation up to 60 minutes. Retinas incubated in the test Ringer's solution showed signs of cellular degeneration in the ganglionic and inner plexiform layers and edema in the inner nuclear, outer plexiform and inner plexiform layers. The administration of 10^{-6} M to 10^{-4} M MK 801 to retinas incubated in test Ringer's caused a dose related improvement in these structural integrity of the retina, with all layers present in the MK 801-treated retinas, when compared to nontreated retinas. In addition, the edema noted in retinas incubated in the test Ringer's was reduced by the administration of MK 801.

Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it will be readily

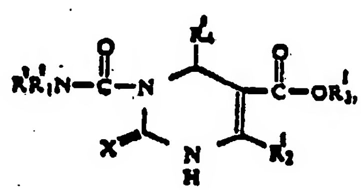
apparent to those of ordinary skill in the art in light of the teachings of this invention that certain changes and modifications may be made thereto without departing from the spirit or scope of the appended claims.

CLAIMS

1. A method of treating a subject suffering from ischemia or edema of the retina or optic nerve which comprises administering to said subject a therapeutically effective amount of a calcium channel antagonist selected from the group consisting of dihydropyrimidones and benzazepines.

2. The method of claim 1, wherein said calcium channel antagonist is a dihydropyrimidone.

3. The method of claim 1, wherein said dihydropyrimidone is of the formula:



and pharmaceutically acceptable salts thereof wherein X is oxygen or sulfur; R' is hydrogen, alkyl, cycloalkyl, aryl, or arylalkyl and R'_1 is hydrogen, alkyl, cycloalkyl, aryl, heterocyclo,

$$-\underset{R'_6}{\overset{R'_5}{C}}-(CH_2)_n-Y_2-\underset{R'_6}{\overset{R'_5}{C}}-(CH_2)_p\longrightarrow Y_3$$

or halo substituted alkyl, or R' and R'_1 taken together with the nitrogen atom to which they are attached are 1-pyrrolidinyl, 1-piperidinyl, 1-azepinyl, 4-morpholinyl, 4-thiamorpholinyl, 1-piperazinyl, 4-alkyl-1-piperazinyl, 4-arylalkyl-1-piperazinyl, 4-diarylalkyl-1-piperazinyl or 1-pyrrolidinyl, 1-piperidinyl, or 1-azeipinyl substituted

with alkyl, alkoxy, alkylthio, halo, trifluoromethyl or hydroxy;

R'_2 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl,

$$-\underset{R'_6}{\overset{R'_5}{\underset{|}{\overset{|}{C}}}}-(CH_2)_n-Y_1,$$

or halo substituted alkyl;

R'_3 is hydrogen, alkyl, cycloalkyl, aryl, heterocyclo,

$$-\underset{R'_6}{\overset{R'_5}{\underset{|}{\overset{|}{C}}}}-(CH_2)_n-Y_2,\ -\underset{R'_6}{\overset{R'_5}{\underset{|}{\overset{|}{C}}}}-(CH_2)_p-Y_3,$$

or halo substituted alkyl;

R'_4 is aryl or heterocyclo;

R'_5 and R'_6 are each independently hydrogen, alkyl, $-(CH_2)_q-$aryl or $-(CH_2)_q-$cycloalkyl;

Y_1 is cycloalkyl, aryl, heterocyclo, hydroxyl, alkoxy, aryl $-(CH_2)_m-O-$, mercapto, alkylthio, aryl$-(CH_2)_m-S-$, amino, substituted amino, carbamoyl,

(Substituted amino)$-\overset{O}{\overset{\|}{C}}-$, heterocyclo$-(CH_2)_m-\overset{O}{\overset{\|}{C}}-$

carboxyl, alkoxycarbonyl, alkyl$-\overset{O}{\overset{\|}{C}}--$, aryl$-(CH_2)_m)-\overset{O}{\overset{\|}{C}}-$

alkyl$-\overset{O}{\overset{\|}{C}}-O-$ or aryl$-(CH_2)_m-\overset{O}{\overset{\|}{C}}-O-$

Y_2 is cycloalkyl, aryl, heterocyclo, carbamoyl,

(substituted amino)$-\overset{O}{\overset{\|}{C}}-$, carboxyl, alkoxycarbonyl,

alkyl$-\overset{O}{\overset{\|}{C}}-$, aryl$-(CH_2)_m-C-$ or heterocyclo$-(CH_2)_m-\overset{O}{\overset{\|}{C}}-$;

Y_3 is hydroxyl, alkoxy, aryl$--(CH_2)_m-O-$, mercapto,

alkylthio, aryl—$(CH_2)_m$—S—, alkyl-$\overset{O}{\overset{\|}{C}}$—O—, aryl-$(CH_2)_m$—$\overset{O}{\overset{\|}{C}}$—O—, amino or substituted amino;

q is 0, 1, 2 or 3;

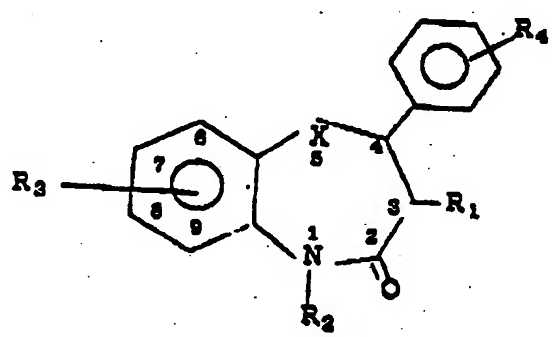
m is 0 or an integer of 1 to 6;

n is 0 or an integer of 1 to 5; and

p is an integer of 1 to 5.

4. The method of claim 3, wherein said dihydropyrimidone is (R)-1-(aminocarbonyl)-6-(3-chlorophenyl)-1,2,3,6-tetrahydro-4-methyl-2-oxo-5-pyrimidine carboxylic acid, 1-methylethyl ester.

5. The method of claim 1, wherein said calcium channel antagonist is a benzazepine of the formula:

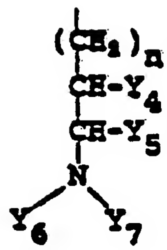
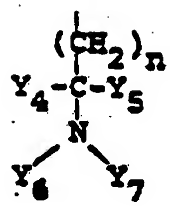
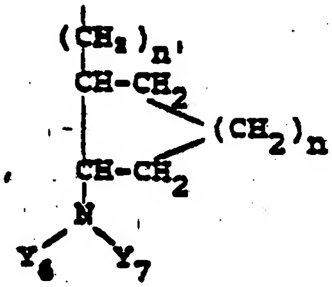


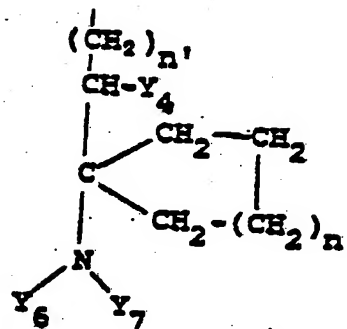
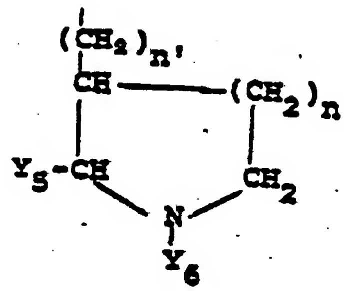
and the pharmaceutically acceptable salts thereof, wherein:

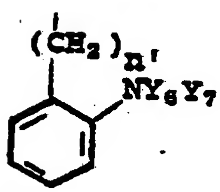
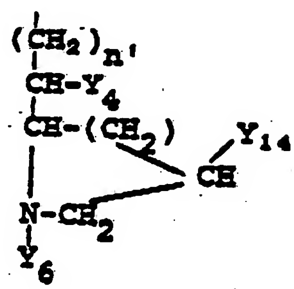
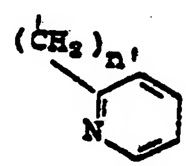
X is $-CH_2-$;

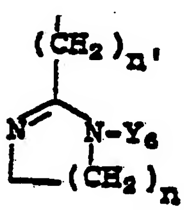
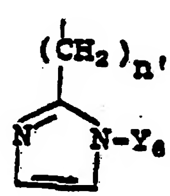
R_1 is $-\underset{Y_2}{\underset{|}{\overset{Y_1}{\overset{|}{C}}}}H$ or $-O-Y_3$;

when X is $-CH_2-$, R_2 is

 ,  ,  ,

 ,  ,

 ,  , 

 , or  ;

R_3 and R_4 are each independently hydrogen, halogen, alkyl, alkoxy, aryloxy, arylalkoxy, arylalkyl, cyano, hydroxy, alkanoyloxy, $-O-\overset{O}{\overset{\|}{C}}-NY_9$, fluoro substituted alkoxy, fluoro substituted alkyl, (cycloalkyl)alkoxy, $-NO_2$, $-NY_{10}Y_{11}$, $-S(O)_m$alkyl, $-S(O)_m$aryl, $-\overset{O}{\overset{\|}{C}}-Y_{12}$ or $-O-\overset{O}{\overset{\|}{C}}-Y_{13}$;

n or n' are independently 0, 1, 2, or 3;

m is 0, 1 or 2;

Y_1 and Y_2 are independently hydrogen or alkyl, Y_1 is hydrogen and Y_2 is alkenyl, alkynyl, aryl, heteroaryl, or cycloalkyl, or Y_1 and Y_2 together with the carbon atom to which they are attached are cycloalkyl;

Y_3 is hydrogen, alkyl, alkanoyl, alkenyl, arylcarbonyl, heteroarylcarbonyl, or $-\overset{O}{\overset{\|}{C}}-NY_8Y_9$;

Y_4 and Y_5 are each independently hydrogen, alkyl, aryl or arylalkyl, provided that when both are present they are not both hydrogen, and provided further that when both are attached to the same carbon atom neither of them is hydrogen;

Y_6 and Y_7 are each independently hydrogen, alkyl, cycloalkyl or arylalkyl or Y_6 and Y_7 together with the nitrogen atom to which they are attached are azetidinyl, pyrrolidinyl, piperidinyl, or morpholinyl;

Y_8 and Y_9 are each independently hydrogen, alkyl, aryl or heteroaryl, or Y_8 and Y_9 together with the nitrogen atom to which they are attached are pyrrolidinyl, piperidinyl or morpholinyl;

Y_{10} and Y_{11} are each independently hydrogen, alkyl, alkanoyl, arylcarbonyl, heteroarylcarbonyl,

or $-\overset{\displaystyle O}{\overset{\|}{C}}-NY_8Y_9$;

Y_{12} is hydroxy, alkoxy, aryloxy, amino, alkylamino or dialkylamino;

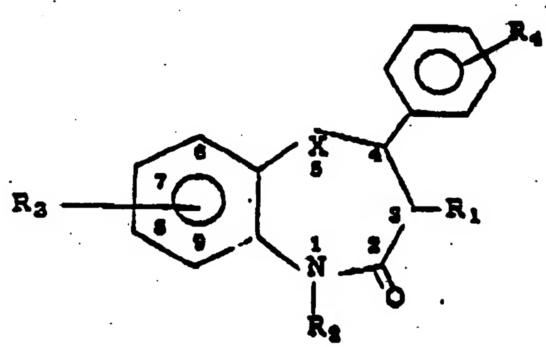
Y_{13} is alkyl, alkoxy, or aryloxy; and

Y_{14} is hydrogen, hydroxy, alkoxy, aryloxy or arylalokoxy.

6. The method of claim 5, wherein said benezazepine is selected from the group consisting of [3R-[1(S*),3<a,4<a]]-3-(Acetyloxy)-1,3,4,5-tetrahydro-4-(4-methoxyphenyl)-1-(2-pyrrolidinylmethyl)-6-(trifluoromethyl)-2H-1-benzazepin-2-one, monohydrochloride.

7. The method of claim 1, wherein said benzazepine is (3R-<u>cis</u>)-3-(Acetyloxy)-1-[2-(dimethylamino)ethyl]-1,3,4,5-tetrahydro-4-(4-methoxyphenyl)-6-(trifluoromethyl)-2H-1-benzazepin-2-one, monohydrochloride.

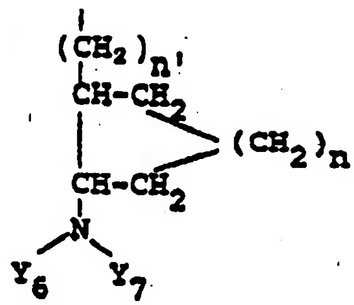
8. A method of treating a subject suffering from ischemia or edema of the retina or optic nerve which comprises administering to said subject a therapeutically effective amount of a benzothiazepine derivative of the formula:

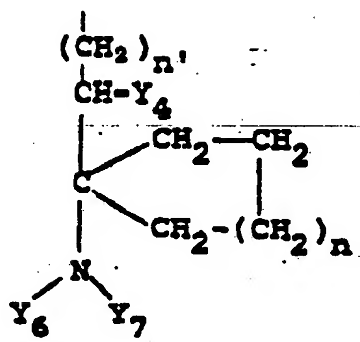
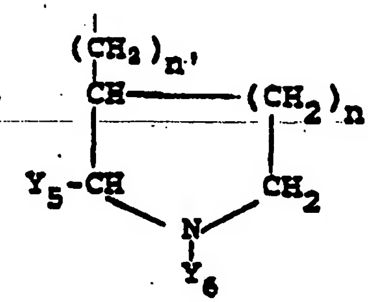


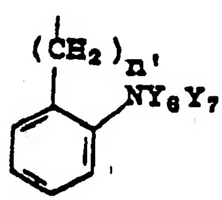
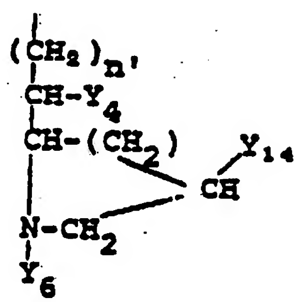
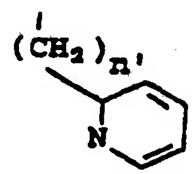
and the pharmaceutically acceptable salts thereof, wherein:

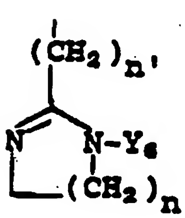
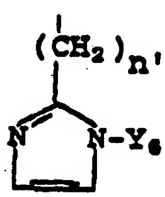
X is -S-;

$$R_1 \text{ is } -\underset{\displaystyle Y_2}{\overset{\displaystyle Y_1}{\underset{|}{\overset{|}{C}}}}H \text{ or } -O-Y_3;$$

R_2 is  ,

 ,  ,

 ,  , 

 , or  ;

R_3 and R_4 are each independently hydrogen, halogen, alkyl, alkoxy, aryloxy, arylalkoxy, arylalkyl, cyano, hydroxy, alkanoyloxy, $-O-\overset{O}{\overset{\|}{C}}-NY_9$, fluoro substituted alkoxy, fluoro substituted alkyl, (cycloalkyl)alkoxy, $-NO_2$, $-NY_{10}Y_{11}$, $-S(O)_m$alkyl, $-S(O)_m$aryl, $-\overset{O}{\overset{\|}{C}}-Y_{12}$ or $-O-\overset{O}{\overset{\|}{C}}-Y_{13}$;

n or n' are independently 0, 1, 2, or 3;

m is 0, 1 or 2;

Y_1 and Y_2 are independently hydrogen or alkyl, Y_1 is hydrogen and Y_2 is alkenyl, alkynyl, aryl, heteroaryl, or cycloalkyl, or Y_1 and Y_2 together with the carbon atom to which they are attached are cycloalkyl;

Y_3 is hydrogen, alkyl, alkanoyl, alkenyl, arylcarbonyl, heteroarylcarbonyl, or $-\overset{O}{\overset{\|}{C}}-NY_8Y_9$;

Y_4 and Y_5 are each independently hydrogen, alkyl, aryl or arylalkyl, provided that when both are present they are not both hydrogen, and provided further that when both are attached to the same carbon atom neither of them is hydrogen;

Y_6 and Y_7 are each independently hydrogen, alkyl, cycloalkyl or arylalkyl or Y_6 and Y_7 together with the nitrogen atom to which they are attached are azetidinyl, pyrrolidinyl, piperidinyl, or morpholinyl;

Y_8 and Y_9 are each independently hydrogen, alkyl, aryl or heteroaryl, or Y_8 and Y_9 together with the nitrogen atom to which they are attached are pyrrolidinyl, piperidinyl or morpholinyl;

Y_{10} and Y_{11} are each independently hydrogen, alkyl, alkanoyl, arylcarbonyl, heteroarylcarbonyl,

or $-\overset{O}{\overset{\|}{C}}-NY_8Y_9$;

Y_{12} is hydroxy, alkoxy, aryloxy, amino, alkylamino or dialkylamino;

Y_{13} is alkyl, alkoxy, or aryloxy; and

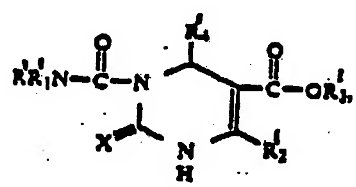
Y_{14} is hydrogen, hydroxy, alkoxy, aryloxy or arylalokoxy.

9. The method of claim 1, wherein said compound is administered topically, parenterally or orally.

10. A method of preventing ischemia or edema of the retina or optic nerve which comprises administering to a subject a prophylactically effective amount of a calcium channel antagonist selected from the group consisting of dihydropyrimidones and benzazepines.

11. The method of claim 10, wherein said calcium channel antagonist is a dihydropyrimidone.

12. The method of claim 11, wherein said dihydropryrimidone is is of the formula:



and pharmaceutically acceptable salts thereof wherein X is oxygen or sulfur; R' is hydrogen, alkyl, cycloalkyl, aryl, or arylalkyl and R'_1 is hydrogen, alkyl, cycloalkyl, aryl, heterocyclo,

$$-\underset{R'_6}{\overset{R'_5}{\underset{|}{\overset{|}{C}}}}-(CH_2)_n- \quad Y_2-\underset{R'_6}{\overset{R'_5}{\underset{|}{\overset{|}{C}}}}-(CH_2)_p-Y_3$$

or halo substituted alkyl, or R' and R'_1 taken together with the nitrogen atom to which they are attached are 1-pyrrolidinyl, 1-piperidinyl, 1-azepinyl, 4-morpholinyl, 4-thiamorpholinyl, 1-piperazinyl, 4-alkyl-1-piperazinyl,

4-arylalkyl-1-piperazinyl, 4-diarylalkyl-1-piperazinyl or 1-pyrrolidinyl, 1-piperidinyl, or 1-azeipinyl substituted with alkyl, alkoxy, alkylthio, hālo, trifluoromethyl or hydroxy;

R'_2 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl,

$$-\overset{R'_5}{\underset{R'_6}{\overset{|}{\underset{|}{C}}}}-(CH_2)_n-Y_1,$$

or halo substituted alkyl;

R'_3 is hydrogen, alkyl, cycloalkyl, aryl, heterocyclo,

$$-\overset{R'_5}{\underset{R'_6}{\overset{|}{\underset{|}{C}}}}-(CH_2)_n-Y_2, -\overset{R'_5}{\underset{R'_6}{\overset{|}{\underset{|}{C}}}}-(CH_2)_p-Y_3,$$

or halo substituted alkyl;

R'_4 is aryl or heterocyclo;

R'_5 and R'_6 are each independently hydrogen, alkyl, $-(CH_2)_q-$aryl or $-(CH_2)_q-$cycloalkyl;

Y_1 is cycloalkyl, aryl, heterocyclo, hydroxyl, alkoxy, aryl $-(CH_2)_m-O-$, mercapto, alkylthio, aryl$-(CH_2)_m-S-$, amino, substituted amino, carbamoyl,

(Substituted amino)$-\overset{\underset{\|}{O}}{C}-$, heterocyclo-$(CH_2)_m-\overset{\underset{\|}{O}}{C}-$

carboxyl, alkoxycarbonyl, alkyl-$\overset{\underset{\|}{O}}{C}-$, aryl-$(CH_2)_m$)-$\overset{\underset{\|}{O}}{C}-$

alkyl-$\overset{\underset{\|}{O}}{C}-O-$ or aryl-$(CH_2)_m-\overset{\underset{\|}{O}}{C}-O-$

Y_2 is cycloalkyl, aryl, heterocyclo, carbamoyl,

(substituted amino)-$\overset{\underset{\|}{O}}{C}-$, carboxyl, alkoxycarbonyl,

alkyl-$\overset{O}{\overset{\|}{C}}$—, aryl-$(CH_2)_m$—$\overset{O}{\overset{\|}{C}}$— or heterocyclo-$(CH_2)_m$—$\overset{O}{\overset{\|}{C}}$—;

Y_3 is hydroxyl, alkoxy, aryl—$(CH_2)_m$—O—, mercapto, alkylthio, aryl—$(CH_2)_m$—S—,

alkyl-$\overset{O}{\overset{\|}{C}}$—O—, aryl-$(CH_2)_m$—$\overset{O}{\overset{\|}{C}}$—O—,

amino or substituted amino;

q is 0, 1, 2 or 3;

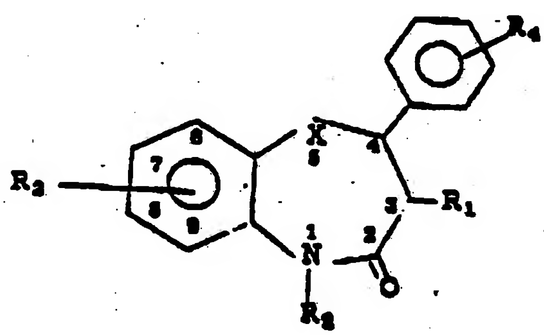
m is 0 or an integer of 1 to 6;

n is 0 or an integer of 1 to 5; and

p is an integer of 1 to 5.

13. The method of claim 12, wherein said dihydropyrimidone is (R)-1-(aminocarbonyl)-6-(3-chlorophenyl)-1,2,3,6-tetrahydro-4-methyl-2-oxo-5-pyrimidine carboxylic acid, 1-methylethyl ester.

14. The method of claim 10, wherein said calcium channel antagonist is a benzazepine of the formula:

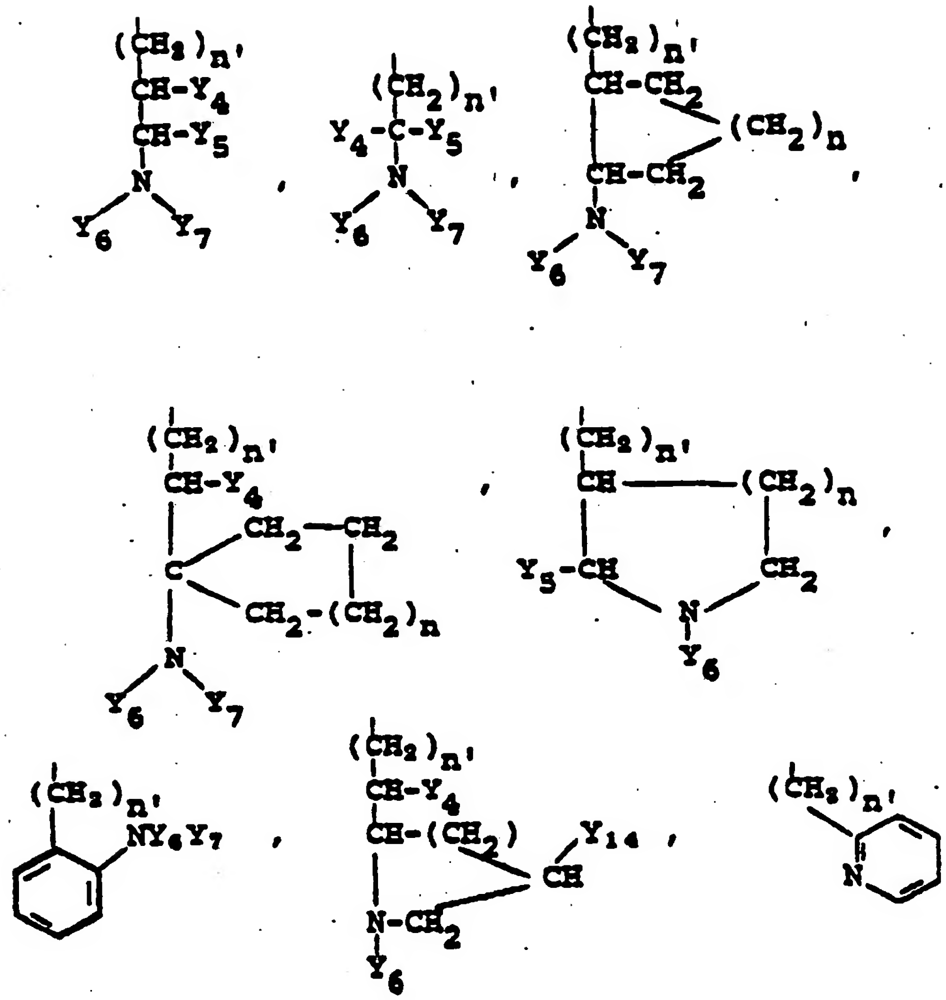


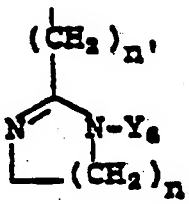
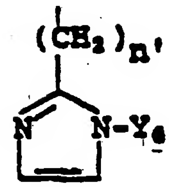
and the pharmaceutically acceptable salts thereof, wherein:

X is $-CH_2-$;

R_1 is $-\underset{Y_2}{\overset{Y_1}{CH}}$ or $-O-Y_3$;

R_2 is



 , or  ;

R_3 and R_4 are each independently hydrogen, halogen, alkyl, alkoxy, aryloxy, arylalkoxy, arylalkyl, cyano, hydroxy, alkanoyloxy,

$-O-\overset{\overset{O}{\|}}{C}-NY_9$, fluoro substituted alkoxy, fluoro substituted alkyl, (cycloalkyl)alkoxy, $-NO_2$, $-NY_{10}Y_{11}$, $-S(O)_m$alkyl, $-S(O)_m$aryl, $-\overset{\overset{O}{\|}}{C}-Y_{12}$ or $-O-\overset{\overset{O}{\|}}{C}-Y_{13}$;

n or n' are independently 0, 1, 2, or 3;

m is 0, 1 or 2;

Y_1 and Y_2 are independently hydrogen or alkyl, Y_1 is hydrogen and Y_2 is alkenyl, alkynyl, aryl, heteroaryl, or cycloalkyl, or Y_1 and Y_2 together with the carbon atom to which they are attached are cycloalkyl;

Y_3 is hydrogen, alkyl, alkanoyl, alkenyl, arylcarbonyl, heteroarylcarbonyl, or $-\overset{\overset{O}{\|}}{C}-NY_8Y_9$;

Y_4 and Y_5 are each independently hydrogen, alkyl, aryl or arylalkyl, provided that when both are present they are not both hydrogen, and provided further that when both are attached to the same carbon atom neither of them is hydrogen;

Y_6 and Y_7 are each independently hydrogen, alkyl, cycloalkyl or arylalkyl or Y_6 and Y_7 together with the nitrogen atom to which they are attached are azetidinyl, pyrrolidinyl, piperidinyl, or morpholinyl;

Y_8 and Y_9 are each independently hydrogen, alkyl, aryl or heteroaryl, or Y_8 and Y_9 together with the nitrogen atom to which they are attached are pyrrolidinyl, piperidinyl or morpholinyl;

Y_{10} and Y_{11} are each independently hydrogen, alkyl, alkanoyl, arylcarbonyl, heteroarylcarbonyl, or $-\overset{\overset{O}{\|}}{C}-NY_8Y_9$;

Y_{12} is hydroxy, alkoxy, aryloxy, amino, alkylamino or dialkylamino;

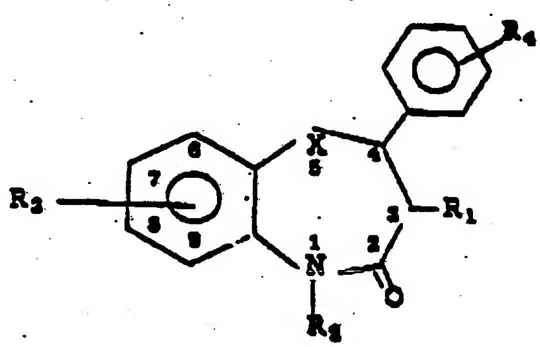
Y_{13} is alkyl, alkoxy, or aryloxy; and

Y_{14} is hydrogen, hydroxy, alkoxy, aryloxy or arylalokoxy.

15. The method of claim 14, wherein said benezazepine is [3R-[1(S*),3<a,4<a]]-3-(Acetyloxy)-1,3,4,5-tetrahydro-4-(4-methoxyphenyl)-1-(2-pyrrolidinylmethyl)-6-(trifluoromethyl)-2H-1-benzazepin-2-one, monohydrochloride.

16. The method of claim 10, wherein said benzazepine is (3R-<u>cis</u>)-3-(Acetyloxy)-1-[2-(dimethylamino)ethyl]-1,3,4,5-tetrahydro-4-(4-methoxyphenyl)-6-(trifluoromethyl)-2H-1-benzazepin-2-one, monohydrochloride.

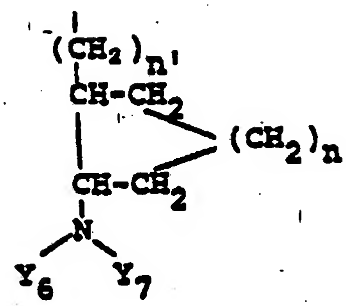
17. A method or preventing ischemia or edema of the retina or optic nerve which comprises administering to a subject a prophylactically effective amount of a benzothiazepine derivative of the formula:

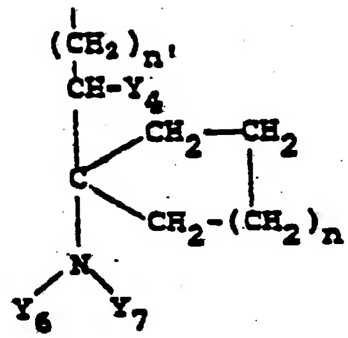
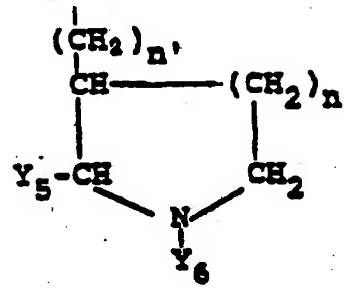


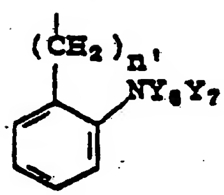
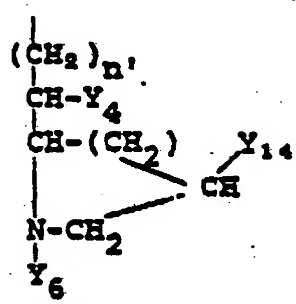
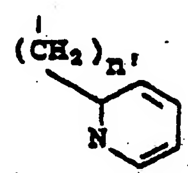
and the pharmaceutically acceptable salts thereof, wherein:

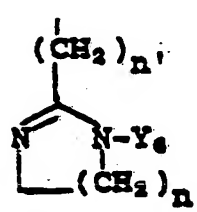
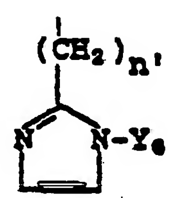
X is -S-;

$$R_1 \text{ is } -\underset{\displaystyle Y_2}{\overset{\displaystyle Y_1}{\mathrm{CH}}} \text{ or } -O-Y_3.$$

R_2 is ,

, ,

, , 

, or ;

R_3 and R_4 are each independently hydrogen, halogen, alkyl, alkoxy, aryloxy, arylalkoxy, arylalkyl, cyano, hydroxy, alkanoyloxy,

$-O-\overset{O}{\overset{\|}{C}}-NY_9$, fluoro substituted alkoxy, fluoro substituted alkyl, (cycloalkyl)alkoxy, $-NO_2$,

$-NY_{10}Y_{11}$, $-S(O)_m$alkyl, $-S(O)_m$aryl, $-\overset{O}{\overset{\|}{C}}-Y_{12}$ or $-O-\overset{O}{\overset{\|}{C}}-Y_{13}$;

n or n' are independently 0, 1, 2, or 3;

m is 0, 1 or 2;

Y_1 and Y_2 are independently hydrogen or alkyl, Y_1 is hydrogen and Y_2 is alkenyl, alkynyl, aryl, heteroaryl, or cycloalkyl, or Y_1 and Y_2 together with the carbon atom to which they are attached are cycloalkyl;

Y_3 is hydrogen, alkyl, alkanoyl, alkenyl, arylcarbonyl, heteroarylcarbonyl, or $-\overset{O}{\overset{\|}{C}}-NY_8Y_9$;

Y_4 and Y_5 are each independently hydrogen, alkyl, aryl or arylalkyl, provided that when both are present they are not both hydrogen, and provided further that when both are attached to the same carbon atom neither of them is hydrogen;

Y_6 and Y_7 are each independently hydrogen, alkyl, cycloalkyl or arylalkyl or Y_6 and Y_7 together with the nitrogen atom to which they are attached are azetidinyl, pyrrolidinyl, piperidinyl, or morpholinyl;

Y_8 and Y_9 are each independently hydrogen, alkyl, aryl or heteroaryl, or Y_8 and Y_9 together with the nitrogen atom to which they are attached are pyrrolidinyl, piperidinyl or morpholinyl;

Y_{10} and Y_{11} are each independently hydrogen, alkyl, alkanoyl, arylcarbonyl, heteroarylcarbonyl, or $-\overset{O}{\overset{\|}{C}}-NY_8Y_9$;

Y_{12} is hydroxy, alkoxy, aryloxy, amino, alkylamino or dialkylamino;

Y_{13} is alkyl, alkoxy, or aryloxy; and

Y_{14} is hydrogen, hydroxy, alkoxy, aryloxy or arylalokoxy.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US89/05505

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC(5): A61K 31/55, A61K 31/50, A61K 31/495, A61K 31/505, A61K 31/535
U.S.: 514/212, 514/252, 514/275. 514/231.5. 514/227.8 514/211, 514/213

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
U.S.	154/212, 514/275, 514/231.5, 514/227.8, 514/252

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

CAS-on line: (Calcium (w) channel:) and (Retin? or Ophthalm?)

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
Y	Avery's Drug Treatment, 3rd edition, pages 683 and 698-700 (1987). See page 683, table II and page 698, column 2 through page 700 column 2.	1-17
Y	Angiology, volume 33, pages 37-45 (1982)Nihard, P., "Effect of Calcium- Entry-Blockers on Arterioles, Capillaries and Venules of the Retina." See page 38.	1-17
Y	Am J Cardiol 1987; 59: 11B-23B, Godfraind, Thephile "Classification of Calcium Antagonists." See page 12B, table 1 and page 13B, figure 2.	1-17
Y	US, A, 4,694,002 (FLOYD ET AL) 15 September 1987 See the abstract	1-17

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
07 MARCH 1990	27 MAR 1990
International Searching Authority	**Signature of Authorized Officer**
ISA/US	RAYMOND J. HENLEY III

See notes on accompanying sheet

Form PCT/ISA/210 (second sheet) (Rev.11-87)